UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,290	05/15/2006	Heinz Vollmers	043043-0359295	7070

27500 7590 06/24/2011

PILLSBURY WINTHROP SHAW PITTMAN LLP
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
06/24/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/579,290	VOLLMERS ET AL.
	Examiner	Art Unit
	LYNN BRISTOL	1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73,80,81,89-91,95-97,106-109,111,112,115,116 and 121-132* is/are pending in the application.

4a) Of the above claim(s) *89-91 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,80,81,106-109,111,112,115,116 and 121-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/7/11 has been entered.

2. Claims 73, 80, 81, 89-91, 95-97, 106-109, 111, 112, 115, 116 and 121-132 are all the pending claims for this application.

3 Claims 73, 106 and 111 were amended and new Claims 125-132 were added in the Response of 3/7/11.

4. Claims 89-91 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

5. Claims 73, 80, 81, 106-109, 111, 112, 115, 116 and 121-132 are all the pending claims under examination.

6. This Office Action contains new grounds for rejection.

Information Disclosure Statement

7. The IDS of 3/7/11 has been considered and entered. The examiner's initialed and signed copy of the 1449 form is attached.

Drawings

8. The replacement drawings for Figures 10A and 10B were received on 7/12/10. These drawings are accepted by the Examiner.

Withdrawal of Objections

Specification

9. The objection to the figure legend to Figures 10A and 10B for failing to describe the x- and y-axis labels for each of the panels is withdrawn.

Applicants' allegations on pp. 9-10 of the Response of 3/7/11 have been considered and are found persuasive.

10. The objection to the amendment to the specification for the incorrect date of hybridoma deposit is withdrawn.

Applicants have corrected the error in the Response of 3/7/11.

Specification/ Sequence Listing

New Matter

11. The objection to the amendment to the specification in the Response of 7/12/10 to change the sequence for the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" as constituting new matter is withdrawn.

Applicants allege on p. 10 of the response of 3/7/11 under *Enzo Biochem* that deposited sequences satisfy written description, and the instant specification describes the recited heavy and light chain variable domains (SEQ ID NOS: 1 and 3). In addition, the statement of Dr. Hensel of 7/12/10 along with the deposit receipts have been reconsidered and entered.

Claim Objections

12. The objection to Claims 109 and 110 for failing to further limit the subject matter of a previous claim is withdrawn. Applicant has cancelled Claim 110 in the Response of 3/7/11.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

13. The rejection of Claims 106 (and new Claim 123) under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any anti-GRP78^{SAM-6} antibody having at least 95% identity to either the VL of SEQ ID NO:1

and/or the VH of SEQ ID NO:3 much less that the antibody variants would have specific and exclusive binding for any one antigen is withdrawn.

Applicants' comments on pp. 11-13 of the Response of 3/7/11 and the attached exhibit D have been found persuasive.

Enablement

14. The rejection of Claims 73, 80, 81, 106-112, 115, 116 and 122-124 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn.

The examiner acknowledges that the ordinary artisan is enabled to *screen* antibodies against the instant claimed cell lines whether of a full antibody format or single variable domain format and comprising an aspect of the VH domain of SEQ ID NO:3. The Declaration of Dr. Vollmers of 11/5/09 has been reconsidered and entered.

Note: Applicants comments on p. 13 of the Response of 3/7/11 including reference to Exhibit B (filed 7/12/10) and Exhibit D (filed 3/7/11) have been considered *but are not* found persuasive in overcoming this rejection. In addition, they are not relevant to the outstanding written description rejections below.

a) The data content of Exhibit B (filed 7/12/10) is of the nature and kind that is required to be filed as a 37 CFR 1.132 declaration, sworn and attested to by a relevant party to the instant claims. Thus Exhibit B has not been entered.

b) The data shown in Exhibit B is not found to be responsive to the enablement rejection. None of the claims require that a VH domain of SEQ ID NO:3 binds to HeLa cells. In fact, the cells intended for binding are recited in Claim 72, and which does not even include He La cells. Under MPEP 2105, the scope of enablement must bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244, 68 USPQ2d 1280, 1287 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971); and *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003).

c) The excerpt in the Response of 3/7/11 from WO 2010/088739 showing the VH domain of SEQ ID NO:3 binding He La cells is post-filing date data from an unrelated application which does not share priority with the instant application nor is the WO reference incorporated by reference. Further, it does not enable the ordinary artisan to make or use the VH domain at the time of filing for the instant application.

Written Description/ New Matter

15. The rejection of Claims 111 and 124 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because Claims 111 and 124 recite new matter being drawn to the VH CDR3 of DEQ ID NO:3 having the following sequence: "Asp-Arg-Leu-Ala-Val-Ala-Gly-Arg-Pro-Phe-Asp- Tyr (CDR3) SEQ ID NO:3" is withdrawn.

Applicants allege on p. 17 of the response of 3/7/11 under *Enzo Biochem* that deposited sequences satisfy written description, and the instant specification describes the recited heavy and light chain variable domains (SEQ ID NOS: 1 and 3). In addition, the statement of Dr. Hensel of 7/12/10 along with the deposit receipts have been reconsidered and entered.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

16. The rejection of Claims 73, 80, 81, 106-109, 11, 112, 115, 116, 121-124 (and new claims 125-132) under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/5/09 as follows:

"Claims 72-79, 82-88 and 98-116 are *interpreted* as being drawn to any antibody that binds the same epitope as the SAM-6 antibody, but which epitope occurs on any number of antigens expressed on the list of neoplastic cells in Claims 72-74 and which antibody may be merely cross-reactive with the SAM-6 epitope. It is the examiner's position that the only antigenic epitope disclosed in the specification as being expressed by the neoplastic cells and recognized by the SAM-6 antibody, is the O-linked carbohydrate moiety on a post-transcriptionally modified isoform of the 78-kDa GRP, designated $GRP78^{SAM-6}$.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: the specification did not reveal the identity of the antigen but generally characterized the antigen by immunohistochemical screening of SAM-6 against normal tissues and autologous tumor where the antigen was defined by the cancer cell-binding properties for the antibody (Example 2). SAM-6 showed no reactivity with normal tissues but different tumor tissues (Tables 3 and 4). Partial characterization of the antigen in Example 3 showed by Western blot analysis the antibody recognized proteins of 140 kDa (Figure 3A). Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08) later described the antigen as GRP78 and the epitope is an O-linked carbohydrate moiety.

b) Disclosure of drawings or structural chemical formulas: the specification and

drawings do not show that applicant was in possession of the epitope on any antigen other than the $GRP78^{SAM-6}$ protein and to which the SAM-6 antibody binds.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the epitope for the genus antigens against which any antibody could be generated and to which SAM-6 antibody binds.

d) Method of making the claimed invention: the specification teaches making and screening antibodies and selecting the SAM-6 antibody, where as evidenced by Rauschert et al (Lab. Invest. 88:375-386 (2008); cited in the PTO 892 form of 9/19/08), the antigen was identified as GRP78 and the epitope is an O-linked carbohydrate moiety.

e) Level of skill and knowledge in the art: The term “specific” binding is not an absolute, in other words, the claimed antibody is not excluded from being cross-reactive for binding the same epitope also recognized by the SAM-6 antibody. It is noted that the term “specific binding” is not used in the immunological arts to connote exclusive binding. “Specifically binds” is not art-defined as exclusive binding as evidenced by Bost et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) “Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin". Specificity of antibody interaction with epitopes is defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific. Applicants have not demonstrated with sufficient evidence the uniqueness or exclusiveness of any antibody recognizing and binding to the epitope on any antigen where the same epitope is recognized by the SAM-6 antibody. .

f) Predictability in the Art: Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth*

Alonso October (Fed. Cir. 2008)) sustaining a lack of adequate written description rejection where "the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies" where the specification does not characterize the antigens to which the monoclonal antibodies must bind).

Applicants have not characterized the epitope occurring on any antigen to which the claimed antibody should specifically and exclusively bind, and therefore, the ordinary artisan could reasonably conclude that Applicants were in possession of the claimed genus of antibodies."

The rejection was maintained in the Office Action of 1/12/10 as follows:

"Applicants allegations on pp. 13-26 have been carefully considered and they are not found persuasive. The gist of the arguments is finally presented on p. 18 when Applicants address Alonso. Here they allege In contrast to the antibodies of Alonso, the claimed antibodies and functional fragments have identical specificity and bind to an epitope, namely the epitope of the antigen expressed by at least one of the specified neoplastic cells recited in the claims to which the SAM-6 antibody comprising SEQ ID NO: 1 and SEQ ID NO:3 specifically binds. Also in contrast to Alonso, the claimed antibodies and functional fragments bind to antigen expressed by at least one of 5 well defined deposited cell lines, namely BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 20 i), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU- NHgl (DSMZ Accession No. ACC 393) neoplastic cells.

Response to Arguments

To put it succinctly, what is the identity of the antigen(s) that places Applicants in possession of "the purified antibody" having all of the following properties:

a) binds exclusively to the same epitope on the same antigen as the SAM-6 antibody;

b) inhibits cell proliferation of 23132/87 (DSMZ Accession No. ACC 20l) cells;

c) induces apoptosis of at least one of BXPC-3 (ATCC Accession No. CRL-1687) and 23132/87 (DSMZ Accession No. ACC 201) cells; and

d) has 80%, 85%, 90% or 95% identity to the VH/VL of SAM-6 antibody?????

Applicants present "specific" binding to some alleged shared antigen amongst several cell lines and to which the "purified antibody" and the "SAM-6 antibody" binds in terms of an absolute, in other words, that the purified antibody binds only some antigen of interest albeit undefined (expressed by at least one of BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), or LOU-NH91 (DSMZ Accession No. ACC 393) .neoplastic cells) to which SAM-6 also binds, and not any other antigen or anywhere else on the cells lines. Applicants allege that one skilled in the art would know that the term excludes cross-reactive antibodies. It is noted that the term "specific binding" is not used in the immunological arts to connote exclusive binding. "Specifically binds" is not art-defined as exclusive binding as evidenced by Bost

et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) "Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin". Applicants' argument attempts to limit the term "specifically binds" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. Consequently, it was well known in the art at the time the invention was made that antibody binding of distinct proteins was indeed specific.

Furthermore, the specification does not define the term "specificity", the binding affinities for the prophetic purified antibodies. Applicants have not demonstrated with sufficient evidence the uniqueness or exclusiveness of any claimed purified antibody recognizing and binding to the same epitope of the same antigen as the SAM-6 antibody.

The rejection was maintained in the Office Action of 1/12/10 as follows:

"Applicants allegations on pp. 15-23 have been considered and are not found persuasive. Applicants allege given the totality of: Guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the light and heavy chain variable region sequences (SEQ 1D NOs: 1 and 3) and the predicted CDRs and FRs that confer binding, as also corroborated by the Exhibit B submitted herewith and the previously submitted Exhibits and Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:l and 3 having binding activity, the claims meet the written description standard articulated by the court in Invitrogen. Further in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2003 compared to 1988, and that the claimed antibodies and fragments will

have the specificity of SAM-6 antibody comprising SEQ ID NOs: I and 3, and will also necessarily have sequence homology with SEQ ID NOs: I or 3, the facts of the claims under consideration are clearly distinguishable from the facts in Alonso.

Response to Arguments

For purposes of brevity and in the interest of compact prosecution, Applicants are directed to the following source materials as guidance for the requirements in meeting written description support under 112, 1st paragraph:

a) Applicants' are requested to visit the Cabic.com website or the USPTO website where they can review any of the past Biotech Customer Partnership (BCP) presentations by TC1600 on subject matter related to claiming antibodies (e.g., structure/function correlation) and meeting written description.

b) See, for example, *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc) stating in part:

> "a few broad principles hold across all cases"; "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Conversely, we have repeatedly stated that actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008), or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)."
>
> "For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus."

c) MPEP 2144.08 states in part:

"In the area of biotechnology, an exemplified species may differ from a claimed species by a conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid... [which] is generally expected to lead to

either no change or only a small change in the properties of the protein." Dictionary of Biochemistry and Molecular Biology 97 (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)."

d) See for example*, Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."; "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004))."

Applicants' allegations on pp. 13-16 of the Response of 3/7/11 have been considered and not found persuasive.

a) Applicants allege WO 2010/088739 discloses numerous sequence variants, fragments (scFV, diabodies) and isotype switched forms of SAM-6 that bind to antigen. In this published application, variants and fragments that bind to target were produced based in part on the knowledge in the art concerning antibody structure correlating with function at the time of the invention combined with skillful selection of one or more amino acid substitutions or fragments.

Response to Arguments

The excerpt in the Response of 3/7/11 from WO 2010/088739 showing the VH domain of SEQ ID NO:3 binding He La cells is post-filing date data from an unrelated

application. Applicants would urge the Office to believe that because the single VH domain (SEQ ID NO:3) and a scFv of VH/VL (SEQ ID NO: 1/3) can bind He La cells, that any antibody having the same VH CDRs and variants thereof (or VL CDRs and variants thereof) would also share the same functional characteristics to those instantly claimed. Applicants had not even defined the antigen or epitope common to all of the claimed cell lines at the time of filing. Most notably, He La cells from WO 2010/088739 have not been demonstrated as comprising the same epitope/antigen on the claimed cells BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393). The examiner re-states and re-iterates that Applicants have not demonstrated a specifically binding antibody from a cross-reactive antibody for a yet-to-be discovered antigen.

b) Applicants allege neither Ariad nor any other controlling case law requires an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. In re Angstadt, 537 F.2d 498, 502-503…"

Response to Arguments

It has been well known that minor structural differences even among structurally related compounds can result in substantially different binding activities for the same antibody. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991)) disclose that a single amino acid substitution in a common allele ablates binding of a

monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980)) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document). The examiner submits that the antigen shared or common amongst the claimed cell lines much less the He La cell line has/have not even been characterized much less has its identity been addressed by Applicants at this point in the prosecution proceeding.

Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008) sustaining a lack of adequate written description rejection where "the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies" where the specification does not characterize the antigens to which the monoclonal antibodies must bind). Applicants have not characterized a representative species of antibody falling within the genus of antibodies binding to the shared epitope/antigen amongst the claimed cell lines. Applicants have not shown that a reasonable number of species of antibodies would specifically bind the same antigen even if the antigen were known much less disclosed.

c) Applicants allege the skilled artisan would also have known residues within SEQ ID NOs: 1 and 3 more and less amenable to substitution. Consequently, one skilled in the art could have been able to predict with a high degree of confidence many substitutions of SEQ ID NOs:l and 3 that would not destroy binding activity, as corroborated by the numerous SAM-6 sequence variants, fragments (scFV, diabodies) and isotype switched forms described in WO 2010/088739 that bind to antigen.

Response to Arguments

The examiner submits that knowing the identity of the antigen is a critical feature of this invention in order to place applicants in possession of the myriad antibodies. See for example MPEP 2163 stating in part:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art."

"The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

MPEP 2163.05 stating in part:

"A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement."

Applicants have failed to show the existence of appropriate epitopes/regions of any target antigen for any of the claimed cell lines that would provide the claimed functional properties required of the antibody. The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004). A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit the required claimed functional properties. There is insufficient guidance and direction as to the written description of the claimed antibody, as broadly encompassed by the claimed invention. Given the well known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention; one of skill in the art would conclude that applicant was not in possession of the functional attributes of a representative number of species possessed by the members of the genera and broadly encompassed by the claimed invention. One of skill in the art would conclude that the specification fails to

disclose a representative number of species much less a single species to describe the claimed genera where the specification has not even characterized the antigen.

d) Applicants allege in contrast to *Noelle* which disclosed no human CD40CR antibody, the variable region sequences (SEQ ID NOs:1 and 3) of an exemplary antibody are disclosed in Applicant's specification, and given the substantial knowledge of structure/function correlations in the antibody art at the time of the invention, one skilled in the art could produce variant antibodies and fragments that would likely retain binding activity.

Response to Arguments

Applicants own admission of record on p. 16 of the Response of 3/7/11 is that in *Noelle*, the murine antigen for the murine antibody was known (CD40CR). Here in contrast to *Noelle*, none of the epitope(s)/antigen(s) on the claimed cell lines and recognized by the VH/VL of SEQ ID NOS: 1 and 3 has been disclosed, much less which of the myriad antibody variants would also predictably and specifically recognize and bind the same epitope(s)/antigen(s) on the claimed cells lines.

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

17. Claims 73, 107, 108, 112, 115, 116, 121-124, 127, 131 and 132 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is the examiner's position that the specification does not support a single variable domain of SEQ ID NO:3 or derived from SEQ ID NO: 3 and binding a wholly uncharacterized target antigen expressed on the cell lines: BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), or LOU-NH91 (DSMZ Accession No. ACC 393).

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: There are no working examples in the

specification as filed disclosing a single isolated human antibody comprising a VH of SEQ ID NO:3 much less variants thereof much less which bind the cell lines of the instant claims.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the myriad antibody variants of a single variable domain of or derived from SEQ ID NO: 3.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with *correlation between structure and function* for the genus of the myriad antibody variants for a single variable domain of or derived from SEQ ID NO: 3 and binding the cell lines of the instant claims.

d) Method of making the claimed invention: the specification teaches making a single human antibody from human lymphocyte sources and fusing into a trioma. The single SAM-6 antibody was selected and characterized based on its binding to the instant claimed cell lines.

e) Level of skill and knowledge in the art: the selection of antibodies, cloning of antibody DNA, protein sequencing, and performing bioassays for identifying functional regions or functional properties was well established at the time of the invention.

f) Predictability in the Art:

i) Applicants have not characterized a representative species of antibody falling

within the genus of antibodies meeting the instant claimed structure/function requirements to place Applicants in possession of the variant antibody species at the time of filing. The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See *University of Rochester v. G.D. Searle & Co., Inc.,* 69 USPQ2d 1886,1895 (Fed. Cir. 2004. A skilled artisan cannot visualize or recognize the identity of the members of the genus of antibody that have no defined antigen as in the instant claims.

Centocor Ortho Biotech Inc. v. Abbott Labs., No. 2010-1144 (Fed. Cir. 2/23/2011) where the Federal Circuit noted that the specification only included a mouse variable region and did not disclose a single human variable region. The court further stated that Centocor's mouse variable region was "very different" from the sequence of a human variable region like the one in Abbot's fully human antibody, and that the specification does not "disclose any relationship between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations." Therefore, the mouse variable region did not serve as a "stepping stone" to identifying a human variable region within the scope of the claims.

And in *Billups-Rothberg Inc. V. Assoc. Regional and Univ. Pathologists, Inc.* (Fed. Cir. 2011), Billups disclosed only the approximate location of the relevant mutation

in a patent, a disclosure that it argued was sufficient to place the inventor in possession of the invention (which in this case included the step of detecting the mutation) when combined with the knowledge that existed at the time of invention. The CAFC disagreed. "Given the lack of knowledge of sequences for the hemochromatosis gene and its mutations in the field, the limited extent and content of the prior art, and the immaturity and unpredictability of the science when the patent was filed, Billups cannot satisfy the written description requirement merely through references to later-acquired knowledge."

ii) It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979) teach that the alteration

of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

IN the instant case, the claims encompass antibodies comprising less than the full complement of VH/VL CDRs. Applicants have not shown that any antibody comprising less than a full complement of VH/VL CDRs from a parent antibody would retain the antigen binding for HER2 and VEGF. In fact there are numerous publications acknowledging that the conformation of CDRs as well as FR influence binding.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745); cited in the PTO 892 form of 9/19/08), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

De Pascalis *et al.* (The Journal of Immunology (2002) 169, 3076-3084); cited in the PTO 892 form of 9/19/08) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* ((2003) BBRC

307, 198-205); cited in the PTO 892 form of 9/19/08), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* ((2002) J. Mol. Biol. 320, 415-428); cited in the PTO 892 form of 9/19/08) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* ((2007) Mol. Immunol. 44: 1075-1084); cited in the PTO 892 form of 9/19/08) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. (1999) 293, 865-881); cited in the PTO 892 form of 9/19/08) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. (1999) 294, 151-162); cited in the PTO 892 form of 9/19/08) state that it is difficult to predict which framework residues serve a critical role

in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Additionally, the data seem to indicate that it is the frameworks and CDRs that contribute to antigen binding.

iii) The claims encompass single variable domain antibodies which are unpredictable in binding.

The single domain antibodies taught in WO 2004/003019 (Domantis); cited in the PTO 892 form of 9/10/10) and Ward et al. (Nature 341:544-546 (1989); cited in the PTO 892 form of 9/10/10) appear to be limited examples of single domain antibodies generated against a limited number of antigens that have been shown to retain antigen binding specificity. However, Ward teaches and cautions:

"Separated heavy and light chains have previously been identified with antigen or hapten binding activities although the affinities were poor, with no evidence for binding by single chains rather than dimers" (p. 544, Col. 2) and

"However, VH domains are relatively sticky, presumably due to the exposed hydrophobic surface normally capped by the VH and VL domains" (p. 546, Col. 1).

By and large, the art recognizes that single domain antibodies do not provide the sufficient contact sites for antigen binding or at the very least the molecules tend to be less soluble and otherwise form aggregates.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987); cited in the PTO 892 form of 9/19/08) observed from chain recombination experiments that through interactions

between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000); cited in the PTO 892 form of 9/19/08) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000); cited in the PTO 892 form of 9/19/08) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for any antigen much less where as here in the instant case, the antigen is unknown, would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Applicants have not characterized a sufficient number of antibodies having the structure depicted in the claims and having the correlated functional properties. Applicants were not in possession of the claimed genus of antibodies meeting all of the structural and functional properties required under the written description guidelines.

Given the well- known high level of polymorphism of immunoglobulins /

antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies encompassed by the claimed invention; one of skill in the art would conclude that applicant was not in possession of the functional attributes of a representative number of species possessed by the members of the genera of an antibody which have an unknown binding antigen.

Conclusion

18. No claims are allowed.

19. The VL (SEQ ID NO:1) and VH (SEQ ID NO:3) domains of the SAM-6 antibody are free from prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner, Art Unit 1643